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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

005609
RELEASABLE

DEC - 5 1986

MEMORANDUM

SUBJECT: Review of linuron rabbit developmental toxicity study; Acc. # 260064; Caswell 528; EPA I.D. # 035506; Project 891

TO: Ingrid Sunzenauer, Review Manager
Special Review Branch (TS-767C)

and

Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: James N. Rowe, Ph.D.
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Hazard Evaluation Division/HED (TS-769C)
James N. Rowe 12/1/86

THRU: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
Toxicology Branch/HED (TS-769C)
LDC 12/1/86
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch/HED (TS-769C)
12/5/86

ACTION REQUESTED: Review of duPont linuron dose-ranging study and full rabbit developmental toxicity study (Acc. # 260064); EPA I.D. # 035506

CONCLUSIONS/RECOMMENDATIONS:

Probe study:

Administration of linuron during days 7 through 19 of the gestation period in New Zealand white rabbits produced a dose-dependent effect upon maternal toxicity (mortality, clinical changes, body weight depression, food consumption, increased liver weights) with some toxicity observed at the lowest dose utilized (50 mg/kg/day). Developmental toxicity (decreased mean litter size, decrease in the number of implantations, decrease in number of viable fetuses/doe, decreased uterine weights, depressed fetal weights) was primarily observed in the 200 mg/kg/day group, although mean uterine weights were lower than controls at all dose levels and mean fetal weights were depressed in both the mid and high dose group. Based on this study doses of 5, 25 and 100 mg/kg/day were utilized in the main teratology study. This study was not designed to fulfill the requirements for a rabbit developmental toxicity study and is designated as Core Supplementary data.

Excerpts of data submitted by registrant are included with this memo (pp. 1-)
These pages may be requested by writing Freedom of Information (A-101), EPA, Washington D.C. 20460. Requests should be addressed to Sam or Afformation of Non-multinational Status.

DEVELOPMENTAL TOXICITY STUDY:

Linuron administered at dose levels of 0, 5, 25 and 100 mg/kg to pregnant New Zealand White rabbits during days 7-19 of gestation produced evidence of maternal toxicity including an increase in the abortion rate (high dose), a dose-related depression on maternal body weight (mid, high dose), a decrease in food consumption (high dose) and significant depression of the maternal liver weights and liver/body weight ratios (high dose). The maternal toxicity NOEL is determined to be 5 mg/kg/day. There was evidence of fetal toxicity from linuron administration based on the high dose effects (decrease in mean number of fetuses/litter and mean fetal weight). However a developmental toxicity NOEL was not established based on a statistically significant trend in the elevation of total skull alterations observed in the fetuses of treated groups. There was also a pair-wise statistically significant elevation of total fetal findings or a borderline significant elevation ($.05 < p < .10$) for the dams with fetuses with skull changes at the low dose, as well as statistically significant elevations in the high dose group (litter incidences, % fetal findings).

This study is classified as Core Minimum data. However, since the study failed to establish a NOEL for fetal skull anomalies, a new study is recommended.

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DATA EVALUATION RECORD

STUDY TYPE: Dose-ranging rabbit study for developmental toxicity study

CHEMICAL: Linuron (INZ- 326); N'-(3,4-dichlorophenyl)-N-methoxy-N-methyl-urea; % a.i. not stated

TEST MATERIAL: Linuron (INZ-326; H-14,703; MR #7560) was administered via gavage in an aqueous 0.5% hydroxypropylmethylcellulose suspension at a dosage volume of 5 ml/kg/day.

STUDY I. D.:

a. Title: Dosage-range developmental toxicity study of INZ-326 administered via gavage to New Zealand White rabbits

b. Laboratory: Argus Research Laboratories, Inc.
935 Horsham Road
Horsham, Pennsylvania 19044

c. Study #: Pilot study 104-009P

d. Date of report: September 16, 1985

e. Study Director/Study Monitor: Dr. Alan M. Hoberman/Dr. Robert E. Staples

f. Caswell # 528; Accesssion # 260064; EPA I.D. # 035506

METHODS:

Linuron was administered via gavage to artificially inseminated New Zealand rabbits on day 7 through 19 of presumed gestation at dosages of 0, 50, 100 or 200 mg/kg/day. The percent active ingredient was not specified. The administered volume was adjusted daily on the basis of observed body weights. Maternal body weights were recorded on days 0 and 7 of gestation. Feed consumption was recorded on days 0 through 29 of the study. On day 29, surviving rabbits were killed with T-61® Euthanasia Solution. Laparotomies were performed; the liver was removed and weighed. Corpora lutea present in each ovary were counted. The uterus was removed, weighed and then examined for number, placement and viability of implantations. Fetuses were removed from each uterus and placed in individual containers. The fetuses were then weighed and examined for gross external alterations. Clinical signs were also recorded during the study. All animals were necropsied, either during the study (died, aborted and sacrificed) or at scheduled sacrifice.

Comments:

1. Percent a.i. not indicated in probe study but stated in full study.

2. Artificial insemination procedures not discussed in probe study but presented in full study.

RESULTS/CONCLUSIONS:

In the high dose group (200 mg/kg), 3/6 pregnant does died with 2/6 in the mid dose (100 mg/kg) and 1/6 in the low dose group (50 mg/kg) aborted and being subsequently sacrificed. Two of the rabbits dying at the high dose level had significant ulcerative lesions of the stomach and one had a discolored and enlarged liver. One of the 2 does sacrificed in the 100 mg/kg/day group had nodules on the cardiac and diaphragmatic lobes of the lungs. Paraovarian cysts were a common finding in all test groups.

The clinical observations suggested a dose-related toxicity in the mid and high dose groups. Material, identified in the report as a red substance and which was attributed to increased resorption, was reported in the cage pan at increased incidences in the high dose group (13 days/2 does vs no observations in 3 controls). Anorexia was also increased in the 200 mg/kg/day does and an increased incidence of dried feces was reported in both the mid (13 days/4 does) and high dose group (26 days/4 does) as compared to a single siting on one day with one doe in the control. The increase in dried feces was associated with a decrease in food consumption in the two upper doses. Mean uterine weights were depressed at all dose levels.

There was a dose-related decrease in mean maternal body weights during the period of gestation in the treated animals. During days 7-20 there was a +0.17 kg/kg body weight increase in the control does as compared to -0.17, -0.31 and -0.61 kg/ body weight decrease in the 50, 100 and 200 mg/kg/day dose groups, respectively. Following the dosing period there was a modest weight-rebound in the compound-treated animals during days 20-29 with average values of +0.14, +0.15 and +0.46 kg/B.W., respectively. Average maternal food consumption was also depressed in a dose-related manner during the treatment period and rebounded significantly during the post-treatment period.

The high dose level produced a significant decrease in the mean litter size, early resorptions, number of implantations, and number of does with viable fetuses as compared with the control group (2.3 vs 9.8/con., 2.3 vs 0/con., 4.7 vs 9.8/con., 1 vs 5/con., respectively). There was an apparent increase at all dose levels in the number of does with some resorptions as compared to the controls (2/3-low, 2/4-mid, and 2/3-high vs 0/5 in the control). Mean liver weights were increased in the high dose group as well as an apparent decrease in their mean uterine weights (although the uterine weight observation is only based on one doe) as compared to the controls. Mean fetal body weights were depressed at the mid and high dose levels as compared to the controls (33.2 g/mid and 35 g/high vs 43.48 g/con.). No gross pathological change was reported for any fetus.

Administration of linuron during days 7 through 19 of the gestation period in New Zealand white rabbits produced a dose-dependent effect upon maternal toxicity (mortality, clinical changes, body weight depression, food consumption, increased liver weights) with some toxicity observed at the lowest dose utilized (50 mg/kg/day). Developmental toxicity (decreased mean litter size, decrease in the number of implantations, decrease in number of viable fetuses/doe, decreased uterine weights, depressed fetal weights) was primarily observed in the 200 mg/kg/day group, although mean uterine weights were lower than controls at all dose levels and mean fetal weights were depressed in both the mid and high dose group. Based on this study doses of 5, 25 and 100 mg/kg/day were utilized in the main teratology study. This study was not designed to fulfill the requirements for a rabbit developmental toxicity study and is designated as Core Supplementary data.

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DATA EVALUATION RECORD

STUDY TYPE: Rabbit developmental toxicity study (via gavage)

CHEMICAL: Linuron (INZ- 326); N'-(3,4-dichlorophenyl)-N-methoxy-N-methyl-urea

TEST MATERIAL: Linuron (INZ-326; H-15,851; MR #7560-001) was a light brown powder. Dosage suspensions of test substance (purity 96.2%) in an aqueous 0.5% hydroxypropylmethylcellulose suspension were prepared daily; all concentrations were adjusted to 100% purity. The suspensions were prepared at concentrations of 0 (vehicle), 1, 5 and 20 mg (a.i.)/ml in order to give respective dosages of 0, 5, 25 and 100 mg/kg/day at a dosage volume of 5 ml/kg/day.

STUDY I. D.:

a. Title: Developmental toxicity study of INZ-326 administered via gavage to New Zealand White rabbits

b. Laboratory: Argus Research Laboratories, Inc.
935 Horsham Road
Horsham, Pennsylvania 19044

c. Study #: Protocol 104-009

d. Date of report: September 16, 1985

e. Study Director/Study Monitor: Dr. Alan M. Hoberman/Dr. Robert E. Staples

f. Caswell # 528; Accesssion # 260064; EPA I.D. # 035506

CONCLUSIONS:

Linuron administered at dose levels of 0, 5, 25 and 100 mg/kg to pregnant New Zealand White rabbits during days 7-19 of gestation produced evidence of maternal toxicity including an increase in the abortion rate (high dose), a dose-related depression on maternal body weight (mid, high dose), a decrease in food consumption (high dose) and significant depression of the maternal liver weights and liver/body weight ratios (high dose). The maternal toxicity NOEL is determined to be 5 mg/kg/day. There was evidence of fetal toxicity from linuron administration based on the high dose effects (decrease in mean number of fetuses/litter and mean fetal weight). However a developmental toxicity NOEL was not established based on a statistically significant trend in the elevation of total skull alterations observed in the fetuses of treated groups. There was also a pair-wise statistically significant elevation of total fetal findings of borderline significance ($.05 < p < .10$) for the dams with fetuses with skull changes at the low dose, as well as statistically significant elevations in the high dose group (litter incidences, % fetal findings).

This study is classified as Core Minimum data. However, since the study failed to establish a NOEL for fetal skull anomalies, a new study is recommended.

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METHODS:

A photocopy of the methods section is attached. Review of the experimental methods does not show any unjustified deviation from the 1982 EPA FIFRA Guidelines or Good Laboratory Practices. Discussion of the methods, test material, reagents, processing of animals and associated tissues/fetuses, statistical analysis, etc., and the procedures for the storage and maintenance of raw data are clearly set forth.

RESULTS:

1. Mortality/morbidity/clinical observations

One doe died in the vehicle control during the study period (day 1) due to a reported error during insemination and was replaced in the study, and one doe in the 25 mg/kg/day dose group prematurely delivered and was sacrificed. There was a statistically significant increase ($p<0.05$) in the number of rabbits experiencing soft or liquid feces in the 5 and 25 mg/kg/day dose groups as compared to the vehicle controls (6 does on days 16-29/5 mg and 5 does on days 9-29/25 mg vs 1 control doe on days 26, 27 and 29). There was also a statistically significant increase ($p<0.09$) in the number of rabbits aborting during the study at the 100 mg/kg/day dose as compared to the controls (5 does on days 25, 23, 23, 20 and 20/high dose vs 1 control doe on day 22).

2. Postmortem physical observations

Paraovarian cysts were consistently observed in all dose groups (14 does/control, 10 does/5 mg/kg/day, 18 does/25 mg/kg/day, 15 does/100 mg/kg/day), but were not treatment-related effects.

3. Maternal body weight/body weight gains: (Table 1 and 2 on following page)

Mean absolute maternal body weights (kg) were significantly depressed ($p<0.05$) by day 19 of linuron administration at the high dose level as compared to the control body weights (3.79 kg/high vs 4.07 kg/control) (Table 1). Day 29 corrected body weights did not significantly differ for any dose group.

Mean maternal body weight changes indicated a dose-related effect on body weight during and following compound administration at the mid and high dose levels (Table 2). During days 13-16 there was a slight reduction in relative maternal body gain at the 25 mg/kg/day dose level with a statistically significant decrease at the 100 mg/kg/day dosage as compared to the vehicle control (+.00 kg/mid and -.01 kg/high vs +.08 kg/control). A similar effect was noted during days 16-20 (+.00 kg/mid and -.12 kg/high vs +.02 kg/control). There was a statistically significant ($p<0.05$) rebound in the weight gains for the mid and high dose groups as compared to the vehicle control upon the cessation of compound treatment in does during days 20-24 and which was also observed during the days 24-29, but only statistically significant ($p<.01$) at the high dose, (+.02 kg/mid and +.12 kg/high vs +.03 kg/ control).

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Table 1 : Selected Maternal Body Weights (g) and Maternal Body Weight Changes (kg/stated time period)

treatment group(mg/kg/d)------>	0	5	25	100
Animals treated	25	25	25	25
Pregnant with live fetuses day 29 (N)	20	20	17	13
Maternal body weight (kg)				
Day 7	3.94(±.31)[a]	3.91(±.27)	3.91(±.29)	3.91(±.17)
Day 13	4.00(±.34)	3.98(±.26)	3.98(±.28)	3.90(±.20)
Day 19	4.07(±.36)	4.08(±.26)	3.98(±.32)	3.79(±.28)*
Day 29†	3.72(±.40)	3.70(±.30)	3.67(±.35)	3.65(±.18)

[a] mean ± S.D.; *significantly different from vehicle control by Mann-Whitney U test($p<0.05$); † corrected maternal body weight (day 29 maternal body wt.- gravid uterine wt.)

Table 2: Selected maternal body weight changes (kg/stated period)

treatment group(mg/kg/d)------>	0	5	25	100
Animals treated	25	25	25	25
Pregnant with live fetuses day 29 (N)	20	20	17	13
Maternal body weight change (kg)				
Day 0-7	+.25(±.08)[a]	+.24(±.08)	+.28(±.11)	+.26(±.08)
Day 7-10	+.02(±.04)	+.03(±.04)	+.02(±.04)	+.00(±.06)
Day 13-16	+.08(±.05)	+.09(±.03)	+.04(±.09)	-.01(±.13)*
Day 16-20	+.02(±.07)	+.03(±.05)	[illegible]	[illegible]
Day 20-24	[illegible]	[illegible]	[illegible]	[illegible]
Day 24-29	+.03(±.11)	-.02(±.15)	+.02(±.10)	+.12(±.13)*
Day 20-29	+.05(±.18)	+.01(±.22)	+.11(±.15)	+.26(±.16)**
Day 0-29†	+.02(±.26)	+.03(±.27)	+.05(±.18)	+.00(±.15)

[a] mean ± S.D.; *, ** significantly different from control by Mann-Whitney U test ($p<0.05$; $p<0.01$, respectively); † corrected body wt.(day 29 b.wt.-gravid uterine wt.)

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Table 3: Maternal feed consumption (g/kg b.wt.)

treatment group------> (mg/kg/day)	0	5	25	100
DAYS				
0-7	45.4±(4.5)[a]	45.9(±4.5)	46.5(±4.0)	46.3(±4.3)
7-10	43.9(±3.9)	44.4(±3.3)	45.6(±3.3)	40.6(±11.4)
10-13	41.9(±5.9)	42.2(±6.2)	43.5(±4.1)	32.8(±16.2)
13-16	40.5(±6.0)	42.5(±4.5)	37.6(±13.3)	18.6(±14.9)*
16-20	40.1(±6.0)	42.2(±3.2)	34.3(±13.3)	15.4(±14.4)*
20-24	34.0(±10.8)	37.4(±9.7)	37.3(±9.5)	33.2(±11.1)
24-29	24.1(±11.9)	25.6(±16.4)	32.6(±11.2)	37.8(±6.8)*
20-29	28.5(±10.2)	30.9(±12.3)	35.4(±8.4)	35.9(±8.4)

[a] mean ± S.D.; * significantly different from control by Dunnett's test ($p<0.01$)

4. Maternal food consumption (g/kg/b.wt.): see Table 3 above

Maternal food consumption declined during the treatment period in the high dose group as compared to control food consumption, reaching statistical significance ($p<0.01$) during days 13-16 and 16-20 [High dose(g/kg/b.wt.): 40.6/d 7-10, 32.8/d 10-13, 18.6/d13-16, 15.4/d 16-20 vs Control(g/kg/b.wt.): 43.9/d 7-10, 41.9/d 10-13, 40.5/d13-16, 40.1/d 16-20]. There was a positive rebound in food consumption in the high dose group as compared to the controls during the post-treatment period, which reached statistical significance ($p<0.01$) during days 24-29 (37.8 g/kg/d/high vs 24 g/kg/d).

5. Reproductive/fetal development data: see Table 4 (p.5)

As discussed earlier, linuron produced a significant increase in abortions at the high dose (5) compared to the vehicle control (1). It also produced a decrease in the mean uterine weights (16%; not statistically significant) of high dose dams when compared to the respective control values. There was a statistically significant increase in the mean absolute liver weights of the high dose dams (139.7 g; $p<0.05$) as compared to the control weights (108.3 g). This was reflected in a increase in the mean liver/body weight ratio in the high dose group (3.5) versus that observed in the control dams (2.6).

There was no apparent effect of linuron, at any dose level, on the mean number or percentage of resorptions or the number of dead fetuses. There appeared to be a slight, not statistically significant, decrease at the high dosage in the mean number of fetuses/litter (6.1/high vs 6.8/control) and in the mean fetal weights (41.99 g/high vs 45.83 g/control).

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Table 4: Reproductive and fetal development data (from Table 7 of study)

Treatment group (mg/kg/day)	0	5	25	100
# pregnant/no. inseminated	21/25	20/25	19/25	18/25
# deaths	0	0	0	0
# aborted	1	0	1	5*
# delivered naturally	0	0	1	0
mean # corpora lutea	10.6(±2.0)[a]	10.8(±3.0)	11.6(±2.4)	10.3(±1.5)
mean # implantations	7.2(±2.4)	7.2(±2.8)	7.5(±2.6)	6.5(±2.4)
mean uterine wts(g)	434.8(±121)	415.2(±133)	446.2(±137)	366.6(±132)
mean liver wts(g)	108.3(±24)	114.1(±25)	110.5(±24)	139.7(±22)**
mean liver/body wt ratios (%)	2.6(±0.5)	2.7(±0.6)	2.7(±0.6)	3.5(±0.4)
mean # resorptions†	0.4(±1.0)	0.4(±0.7)	0.4(±0.6)	0.4(±0.8)
mean percentage resorptions†	6.8(±15.3)	5.6(±9.4)	5.8(±12.6)	5.8(±12.6)
# litters with total resorptions†	0	0	0	0
# litters	20	20	17	13
total # fetuses(live+dead)	135	135	121	79
# dead fetuses	0	0	0	0
# live fetuses	135	135	121	79
mean # live fetuses/litter	6.8(±2.6)	6.8(±2.8)	7.1(±2.7)	6.1(±2.4)
mean weight (g)	45.83(±7.9)	44.97(±8.3)	45.54(±6.2)	41.99(±8.2)¶

[a] mean ±S.D.; † excludes rabbits which aborted, delivered, or were not present;
* significantly different from control by Fisher's Exact Test ($p<0.09$);
** significantly different from control by Dunnett's Test ($p<0.05$)
¶ stated in the report (p. IV-3) as not statistically significantly [illegible]
it is not clear as whether this is a typographical error since the level of
statistical significance used in the report is given as [illegible]

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6. Developmental effects: see attached table (Table 8 of report, pgs. A-9 to A-14)

External alterations (exencephaly, flattened head, shortened, umbilical hernia, missing digits, deformed tail) were observed only in the low dose group (5 mg/kg) in five litters (six fetuses total) (see summary Table 8, p. 1 taken from report). Of these alterations, 3/20 litters had one fetus with umbilical hernia. These were not considered significant since they appear to be isolated findings, i.e., not dose- or treatment-related. Visceral examination confirmed the presence of the umbilical hernias.

There was a statistically significant increase ($p<0.01$; Fisher's Exact Test) in the litter incidence for skeletal alterations of the fontanelle (irregularly shaped) reported by the study authors in the high dose group in comparison with the vehicle control litters [1 fetus/1 litter: control vs 16 fetuses/5 litters: high dose] (see attached Table 8, summary of fetal alterations). It appeared appropriate to examine the total skull changes since they are related effects. A summary of total skull changes is presented below:

Total skull alterations:

Dosage group---->	0	5	25	100
# fetuses/# litters	1/1	9/5	5/3	19/6
% dams (malformed fetuses)	5.0**[A]	25.0[b]	17.7	46.2*
total # fetuses examined (% total affected)	135(0.7)**	135(6.7)*	121(4.1)[b]	79(24.2)*
total litters examd.	20	20	17	13

** statistically significant trend in dosed groups for dams with malformed fetuses or % malformed fetuses ($p<0.01$) by Cochran Armitage Trend Test; * statistically significant ($p<0.01$) by Fisher's Exact test; [b] borderline significance ($0.05<p<0.10$) by Fisher's Exact Test; [A] statistical analysis performed by MSS (Mission Support Staff in the Toxicology Branch: refer to attached memorandum)

In addition to the fontanelle changes, linuron also appears to elevate the skull alterations (all alterations combined) in the treated fetuses as compared to the vehicle control animals. The low dose group reported 25% litters with skull changes (borderline statistically significant [$0.05< p <0.10$] by Fisher's Exact test), the mid dose also appeared to have a somewhat elevated incidence of 17.8% and in the high dose 46% of the litters were affected (statistically significant [$p< 0.01$] by Fisher's Exact test) as compared to only 5% (1 litter) in the vehicle controls. The low and high dose group fetal skull malformation incidences (% affected) were statistically significantly different ($p<0.01$) from the control incidences. There was a statistically significant trend ($p<0.001$, 0.01, respectively by the Cochran-Armitage Trend test) between either the number of fetal skull malformations with increasing doses of linuron or the number of dams with fetal skull malformations (litter incidence).

Comparison of the individual findings in the treatment groups against historical litter incidence data (250 litters, 1879 fetuses; data from 1982 to 1984) indicates that all of the treatment-related findings were greater (where findings

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in the controls were observed) than the historical controls.

Non-ossification of the posterior segment of the sternum (xiphoid) appeared to be a consistent finding across all test groups and was not dose- or treatment-related (8 fetuses/6 litters:control; 14 fetuses/6 litters: low; 13 fetuses/7 litters: mid; 8 fetuses/3 litters: high).

DISCUSSION

Administration of linuron via oral gavage at dosages of 0, 5, 25 and 100 mg/kg/day to New Zealand White rabbits during days 7-19 of presumed gestation produced no increase in mortality in the animals. A statistically significant increase in abortions at the high dose (5/18 does), as well as a significant increase in soft or liquid feces at the low and mid dose groups were observed, but not at the high dose. Linuron toxicity in the dams was observed by a dose-related effect on body weight gain during the period of compound administration at the mid and high dose level. The maternal weight gains rebounded positively in these two groups after compound administration was discontinued. Maternal toxicity was also determined on the basis of the statistically significant decline in food consumption (g/Kg b.wt.) at the high dosage during the gestation period which was followed by a positive increase during the post-treatment period. In addition, maternal liver weights were significantly increased at the high dose as reflected by an increase in the liver/body weight ratio.

There was a slight decrease at the high dosage in the mean number of fetuses/litter and in the mean fetal weights. There was a statistically significant increase in the litter incidence for skeletal alterations of the fontanelle (irregularly shaped) reported in the high dose group in comparison with the vehicle control. Examination of the total skull alterations indicates a statistically significant trend (total fetal incidence or litter incidence) for these findings. Pair-wise comparisons against the vehicle controls also indicated borderline or statistically significant elevations in the low dose litter incidences as well as statistically significant elevations in skull alterations in the high dose. Statistical analysis by total fetal incidences (# examined) supported this finding for both dose groups as compared to the vehicle control group.

It is concluded that linuron administered to pregnant New Zealand White rabbits during days 7-19 of gestation produced evidence of maternal toxicity including an increase in the abortion rate (high dose), a dose-related depression on maternal body weight (mid, high dose), a decrease in food consumption (high dose) and significant increase of the maternal liver weights and liver body weight ratios (high dose). The maternal toxicity NOEL is determined to be 5 mg/kg/day. There was evidence of fetal toxicity from linuron administration based on the high dose effects (decrease in mean number of fetuses/litter and mean fetal weight). However a developmental toxicity NOEL was not established based on a statistically significant trend in the elevation of total skull alterations observed in the fetuses of treated groups. There was also a pair-wise statistically significant elevation of total fetal findings or a borderline significant elevation ($.05 < p < .10$) for the dams with fetuses with skull changes at the low dose, as well as statistically significant elevations in the high dose group (litter incidences, % fetal findings).

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This study was conducted properly and has followed the 1982 EPA FIFRA Guideline recommendations for a rabbit developmental toxicity study, therefore it is classified Core Minimum data. However, due to the absence of a developmental NOEL a new study is recommended.